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WilmerHale/Columbia University
399 PARK AVENUE
NEW YORK, NY 10022

EXAMINER	
SINGH, ANOOP KUMAR	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Office Action Summary	Application No.	Applicant(s)	
	10/789,627	KAUFMAN ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7,11-15,18-21,23-27,29,33,35-37,42-44,48-52,54-56,60 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7,11-15,18-21,23-27,29,33,35-37,42-44,48-52,54-56,60 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/15/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments to the claims and arguments filed 11/15/2007 have been received and entered. Claims 2-4, 8-10, 16-17, 22, 28, 34, 38-41, 45-47, 53, 57-59, 61-64 have been cancelled, while claims 1, 5-7, 11, 13, 15, 18-21, 23, 26-27, 29, 33, 35-37, 42-44, 48, 50, 52, 56, 60 and 65 have been amended.

This action is non-Final.

Election/Restrictions

Applicant's election of claims 1-29, 33-61 and 65 (group V) drawn to a composition for delivering a therapeutic agent to a target cell, comprising a microorganism that has on its cell surface an exogenous molecule that binds the target cell and a therapeutic agent wherein the therapeutic agent is a nucleic acid and a method for using said composition in treating neoplasia in the reply filed on April 9, 2007 was acknowledged. Applicants also elected the following species: colon cancer cell, and carcinoembryonic antigen (CEA). In response to additional restriction requirement mailed on 1/28/2008, applicants have elected nucleic acid encoding a polypeptide that is immuno enhancing factor.

Claims 1, 5-7, 11-15, 18-21, 23-27, 29, 33, 35-37, 42-44, 48-52, 54-56, 60, 65 directed to microorganism that has on its cell surface an exogenous molecule that binds the target cell and a therapeutic agent wherein the therapeutic agent is a nucleic acid and method of treating neoplasia using said microorganism is under examination.

Claims 1, 5-7, 11-15, 18-21, 23-27, 29, 33, 35-37, 42-44, 48-52, 54-56, 60, 65 are under consideration.

Oath/Declaration

The Kaufman and Bereta declaration filed on November 15, 2007 under 37 CFR 1.132 is sufficient to overcome the rejection of claims 1, 5-7, 11-15, 18-21, 23-27, 29 based upon the reference of Bereta et al (American association Cancer

Research , 2002, vol. 43, April 6-10, abstract 3288, page 663, IDS), applied under 35 U.S.C. 102(a).

Maintained- New Grounds of Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33, 35-37, 42-44, 48-52, 54-56, 60, 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of targeting neoplastic cells in a subject comprising; (a) administering directly to the neoplastic cells of a solid tumor in a subject an attenuated Salmonella microorganism that has, on its surface, at least one antibody or fragment thereof that binds to a neoplasm- specific antigen on the surface of a neoplastic cell of a solid tumor in the subject: wherein neoplastic cell is a carcinoembryonic-antigen- (CEA)-expressing cell; (b) binding of the attenuated Salmonella to the neoplastic cell; and (c) infecting the neoplastic cell, does not reasonably provide enablement for a method of treating neoplasia in a subject in need of treatment by administering via any route the composition comprising an attenuated Salmonella displaying any other antibody with or without a therapeutic agent comprising gene silencing cassette. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by

weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Applicants' arguments filed 11/15/2007 have been fully considered but are not fully persuasive. Applicants' argument of Salmonella expressing an antibody and administration of attenuated Salmonella for the purpose of tumor targeting is persuasive and therefore rejection pertaining to these issues are withdrawn and indicated in the enabling scope of the rejection. However, applicant's argument with respect to treating any neoplasia including colon cancer with or without therapeutic agent (nucleic acid) and attenuated Salmonella is not persuasive and therefore rejection is maintained in modified form.

Applicants traverse the rejection. With respect to applicants argument that the claimed invention is directed to a composition for delivering an agent to a neoplastic cell of a solid tumor expressing a neoplasm-specific antigen (see page 10 last para. of the arguments), it is noted that instant rejection is not directed to composition claims as argued by the applicants, rather instant rejection is directed to a method for treating neoplasia in a subject in need of the treatment by administering the composition of the invention via any route with a therapeutic

agent that is nucleic acid. It is noted that although instant claims are directed to a method of administering an attenuated Salmonella microorganism that displays CEA antibody on its surface comprising a therapeutic agent that is nucleic acid, they have been analyzed for their intended effect on treating plurality of cancer including colon cancer by delivering nucleic acid that is a plasmid comprising at least one gene silencing cassette.

Applicants argue that an applicants' invention does not have to be actually reduced to practice prior to filing. Further also assert that an applicant is not required to demonstrate that a therapeutic composition is effective and safe for human consumption. *See In re Sichert,* 566 F.2d 1154, 1160 (CCPA 1977). Applicants cite Toso et al. report that "a strain *of Salmonella typhimurium* (VNP20009), attenuated by chromosomal deletion of the purI and msbB genes, was found to target to tumor and inhibit tumor growth in mice [which]... led to the.., phase I study of the intravenous infusion of VNP20009 to patients with metastatic cancer." (Toso et al., (2002) *J Clin Oncol.* 20(1): 142-52, art of record) that use of a human CEA transgenic mouse model as described in the application (see Example 3). Applicants conclude that the state of the art at the time of the invention demonstrate that results obtained using tumorigenic mouse models can be extrapolated to a subject suffering from a cancer.

Applicants' arguments have been fully considered but are not persuasive. As an initial matter, applicants arguments of human safety and efficacy is totally misplaced as it is neither required under statues nor does Examiner has any intention to raise this issue. However, the courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 Ex parte Maizel. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). In the instant case, the issue is whether specification provided adequate guidance so that one of skilled in the art could make and use the

invention. It appears that applicants are arguing that at the time of filing bacterial gene delivery was well established (see page 14 and Medina and Guzman, 2000,Vaccine 1573-80, art of record), however, issue is not limited to delivery of the bacterial vector rather issue at hand is whether administering such therapeutic composition would result in therapeutic effect in treating any cancer or colon cancer as required by the claims. In fact, a general review of art cited by applicants in support of enablement also raise a number of problems associated with the use of live bacterial carriers (see section 5). Furthermore, contrary to applicants argument Toso et al. report that "a strain *of Salmonella typhimurium* (VNP20009) that was capable of inhibiting the growth of tumors in mice by production of nonspecific inflammatory mediators, such as TNF, failed to show any regression in tumor in any of the 24 patient that were administered same VNP20009. In fact, Toso et al states "inability of VNP20009 to fully colonize tumors in patients in our study, despite the administration of high doses of VNP20009, is different than results obtained in rodent tumor models. The factors that account for efficient tumor colonization and preferential accumulation in the rodent tumor models are not fully defined. Differences between the rodent models and patients may exist with regard to entry of bacteria into tumors, growth of the bacteria within the tumors, or clearance from peripheral circulation and from tumors. In our study, we found that clearance of VNP20009 from peripheral blood occurred very rapidly and much faster than clearance in rodents (unpublished data, Vion Pharmaceuticals, New Haven, CT). The rapid clearance from peripheral blood may prevent the delivery of sufficient organisms to the tumor to establish a full infection of the tumor, and administration of higher doses in the 30-minute infusion schedule was precluded by toxicity" (see page 150, col.2). It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).* It is also well established in case law that the specification must

teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994)*, citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991).* Based on disclosure by Toso et al, it is reasonable to state that the tumor bearing rodent model may not be a predictive indicator of probable activity for cytotoxic effects, Kelland et al (European Journal of Cancer, 2004, 40, 827-836, art of record) list several variables that impact on outcome; viz, site of implantation, growth properties of the xenograft and size when treatment is initiated, agent formulation, scheduling, route of administration and dose and the selected endpoint for assessing activity. This in conjunction with disclosure by Toso clearly establishes the unpredictability of the disclosed animal models to be extrapolated to tumor of different etiology and pathology and thus delivery of bacterial vector in a rodent model cannot be directly extrapolated to resulting effect in tumor regression of any other etiology and pathology of any other subject wherein claimed composition is administered via any route in any mammal because it evident that the artisan would require, making and/or using a new invention in the field.

Applicants argue and cite Jain (2001, Expert Opin Biol Ther, 291-300, IDS) and Palffy et al (Gene therapy 2006, 101-105, IDS) to assert that genetic information for specific dsRNA production can be delivered into the target cells via bactofection. Applicants also argues that references of Novina and Paroo show that a person of ordinary skill in the art would have understood that delivery of dsRNA was routine and would not require a person of ordinary skill in the art to engage in undue experimentation because the availability of commercial delivery systems would enable the skilled artisan to routinely screen various nucleic acid concentrations in various cell types using the well-established transfection/infection methods practiced in the art. Therefore, the specification in combination with the state of the art provides reasonable guidance on how to express and deliver a gene-

silencing cassette using the *Salmonella* compositions of the invention with a reasonable expectation of success (see page 15 and 16).

In response, it is emphasized that the issue is not only whether gene silencing cassette could be delivered at the target organ, rather issue is whether gene silencing cassette could be delivered at the target site at level sufficient to have any therapeutic effect. It is generally known in prior art that problems with cancer treatment is due to problems with the complexity and unpredictability of such disorders. Susceptibility and outcome in complex disorders such as cancer are determined, at least in part by genetic polymorphism, and considerable difficulties remain in elucidating how many genes how determine a particular phenotype. The etiology of cancer is multifactorial, and it is likely to involve the actions of genes at multiple levels along the multistage carcinogenesis process. Carbone et al. (Seminars in Cancer Biology, 2004, 14: 399-405) teach: "In the past 40 years, there have been great advances in our understanding of cancer at the cellular and molecular level. ... The prognosis of metastatic carcinoma of the .. breast, prostate, pancreas, liver, etc., has not significantly changed during the past 40 years. This is partly because advanced solid tumors are genetically heterogeneous both among different patients and within the same patient. They are also genetically unstable. The Artisan would not know what gene silencing cassette to deliver to use for the treatment of a disease could be caused by mutations in a number of different genes. .. The use of single agents may often not work very well, due to the complexity of regulatory pathways. The specification does not provide any specific guidance with respect to gene silencing cassettes that could be expressed at therapeutic effective level to treat colon or any other cancer. In the instant case, applicants' amendments to the claims limiting the claims to only attenuated Salmonella strain obviate the basis of tumor targeting by the bacterial vector system, however, the intended effect of the claimed invention in not to target tumor but to treat tumor by delivering any nucleic acid subsequently limiting to gene silencing cassette.

Additionally, as stated in previous office action nucleic acid delivery intended for therapeutic purpose in a mammal at the time of the filing of this application was unpredictable since numerous factors complicate the gene therapy art that is difficult to be overcome by routine experimentation. These include, the fate of nucleic acid, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced. These factors differ significantly based on the vector used and the protein being produced (Ecke et al, Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101, art of record). The specification discloses that the antisense molecules may be generated, synthetically or recombinantly, with a nucleic-acid vector expressing an antisense gene-silencing cassette that may be single-stranded RNAs or DNAs, with lengths as short as 15-20 bases or as long as a sequence complementary to the entire mRNA (see para. 60 of the published application). Additionally, specification contemplated that the double-stranded RNA molecule of the present invention may be very large, comprising thousands of nucleotides; preferably, however, it is small, in the range of 21-25 nucleotides or a double-stranded RNA duplex of at least 19 nucleotides (see para. 62 of the published application). It is noted that recitation of the "nucleic acid comprising a plasmid comprising at least one gene silencing cassette" implies the gene of any length, however the specification does not support the use of the entire gene in an RNAi. In addition, prior and post filing art indicate specific nucleotide length requirements for RNAi to be effective. Elbashir et al (Genes Dev. 2001 15; 15(2):188-200) demonstrates that 21 and 22 mer act as act as guide RNAs for sequence specific mRNA degradation and therefore act most effectively in RNAi. Elbashir et al also describes that 30 bp dsRNA are ineffectively processed to 21-22nt RNA suggesting ineffective gene silencing by larger nucleotide sequence (page188

col. 2, para 2). Therefore, an RNAi sequence or an inverted repeat sequence of the target gene that utilizes the entire sequence of any length would not be predictable in its use in the instant invention. In the instant case, specification dose not provide specific guidance to practice the invention encompassing any plasmid comprising any gene silencing cassette showing contemplated biological activity. The unpredictability of attenuating /inhibiting expression of a target gene in cell by RNAi is evident in prior and post filing art. While it is recognized, that introduction of dsRNA that is targeted to a specific gene may result in attenuation /inhibition of the targeted gene, the degree of attenuation and length of the time attenuation is achieved in not predictable (emphasis added). Caplen et al (Gene 2000, vol. 252, 95-105, art of record) provide evidence of the unpredictability of dsRNA attenuation /inhibition of targeted gene in vertebrate cell *in vitro*. Transient transfection of dsRNA to the βgal transgene into 293 and BHK31 cells resulted in either no effect or a non-specific decrease in gene expression (pp102; Figure 7 A and B). The method disclosed in specification does not provide adequate guidance that sustained expression of transgene could be achieved by administering transgene using any construct comprising polynucleotide of the invention without any tissue specific promoter via any route to any cell of the any species. Thus, as recited gene silencing cassette embrace genus of oligonucleotide, fragments and variants including antisense molecules and DNA or RNA of genomic or synthetic origin that can be single- or double-stranded.

With respect to applicants' argument of delivering genetic information by bactofection, it is noted that even Palffy et al (Gene therapy 2006, 101-105, art of record) assert that "[t]he main problem of bactofection is the possibility of unwanted side effects related to the host-bacteria interactions. The response of the immune system might cause rapid clearance of bacteria or even autoimmune reactions. On contrary, the bacterial strains can acquire the virulence factors back and might cause serious infections" (see page 150, col. 2, para. 2). Therefore, it is apparent that

there were several issues that were not resolved even several years after filing of this application. In any case, Applicant's arguments with respect to delivery of attenuated bacterium are moot in view of modified enabling scope indicated in the rejection.

The specification fails to provide adequate guidance with respect to any gene silencing cassette that could be delivered at the target site and expressed at level sufficient to have any biological effect. Given the lack of disclosure for specific antisense or any other fragment, the skilled artisan would be unable to use the claimed invention without first determining what specific fragment or oligonucleotide or antisense that may be used and then testing whether the specific sequences have an effect on treating any cancer or colon cancer as contemplated by the specification. It is noted that problems related to therapeutic use of nucleic acids, that include antisense were well known in the art at the time of invention (see for example Opalinska et al. (Nature Reviews Drug Discovery 2002). Such problems include the inability of an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. Opalinska et al states "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page: As a general rule, oligonucleotide are taken up primarily through a combination of adsorptive and fluid-phase endocytosis (see page 511). Therefore, it is apparent from the teaching of Opalinska that the level of expression of gene silencing cassette could be critical in achieving contemplated biological effect. Furthermore, art teaches that there are differences in the physiological conditions of a cell *in vitro* as compared to *in vivo* and therefore the uptake and biological activity observed *in*

vitro would not predictably translate into *in vivo* results. Given these teachings, the skilled artisan would not know *a priori* whether *in vivo* delivery of gene silencing cassette by delivering via genetically modified attenuated Salmonella would result in the treatment of any cancer (colon cancer) as embraced by the breadth of the claims. Given, the lack of guidance provided by the specification that it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

Applicants argue that that optimal dose and immunization schedule will vary between species and it would be routine procedure for a person of ordinary skill to determine the administration route and dose of delivery in order to elicit a desired response. Applicants also cite Tosso to report that attenuated strain administered by intravenous infusion to patient with metastatic cancer.

In response, the infection of target cells represents the first critical step in any bacterial gene based therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vehicle. For example, upon systemic administration the vector particle may bind to many cells they encounter *in vivo* and therefore would be diluted before reaching their targets. Examiner has cited art lack of response to non-injected routes such as oral routes, sub lingual, inhalation and vaginal wall due to variation in transfection efficiency (Abstract). Lu et al (Cancer Gene Ther. 1999 Jan-Feb; 6(1):64-72) while reviewing the state of art of efficacy of gene delivery by various routes in prostate describe three routes of delivery (i.t., i.a., and i.v.) to compare in the canine model to determine the transduction efficiency with the lowest systemic dissemination. Lu et al conclude that the different route resulted in variable degree of gene transduction (see page 70, column 2, last paragraph to page 71, column 1, paragraph 1). This is further evident from the teaching of Toso et al that disclose factor such as entry of bacteria into tumors, growth of the bacteria within the tumors, or clearance from peripheral circulation and from tumors also influence the outcome. Thus, it is

apparent that contrary to applicant's assertion it is evident that administration of bacteria via different route would have different clearance rate and thus influencing of therapeutic efficacy. In the instant case, the specification fails to provide any guidance commensurate with full scope of the claimed invention. An artisan would have to perform undue experimentation to make and use the invention without reasonable expectation of success.

In conclusion, in view of breadth of the claims and absence of adequate showing by applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach an *in vivo* method of tumor treatment by administering via any route any microorganism that has one exogenous molecule at its surface and an agent for the treatment of any neoplasia. An artisan would have to carry out extensive experimentation to make and use the invention commensurate with full scope of the claims, and such experimentation would have been undue because art of the gene therapy was not routine rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

Withdrawn-Claim Rejections - 35 USC § 112-Written Description

Claims 1, 5-7, 11-15, 18-21, 23-27, 29, 33, 35-37, 42-44, 48-52, 54-56, 60, 65 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendments to the claims.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 1, 5-7, 11-15, 18-21, 23-27 and 29 rejected under 35 U.S.C. 102(a) as being anticipated by Bereta et al (American association Cancer Research , 2002,

vol. 43, April 6-10, abstract 3288, page 663, IDS) is withdrawn in view of declaration by Drs. Kaufman and Bereta indicating that cited art is not by others.

Claims 1-4, 6-7, 9-11, 25-27 and 29 rejected under 35 U.S.C. 102(b) as being anticipated by Francisco et al (Proc Natl Acad Sci U S A. 1993; 90(22): 10444-8, IDS) is withdrawn in view of amendments to the claims. It is noted that claims have been amended to limit the bacterium to Salmonella that is not disclosed by the cited art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-7, 11-15, 18-21, 23-27, 29, 33, 35-37, 42-44, 48-52, 54-56, 60 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bermudes et al (US patent application no. 20050249706, dated 11/10/2005, effective filing date 10/4/1999) or Szalay et al (US patent application no 20050069491, dated 3/31/2005, effective filing date 7/31/2002), Francisco et al (Proc Natl Acad Sci U S A. 1993; 90(22): 10444-8) and Wu et al. (Immunotechnology,1996, 2:21-36).

It is noted that rejection to claims 33 and 65 is limited to enabling scope of the claims directed to a method for targeting tumor and not to a treatment as embraced by the breadth of claim 33.

Bermudes et al teach an attenuated strain of *Salmonella typhimurium* (VNP 200009 see figure 2) that may comprise effector molecules which are encoded by a

plasmid or transfectable nucleic acid, wherein more than one effector molecule (e.g., primary or secondary) is expressed in an attenuated tumor-targeted bacteria (see para. 60 of the published application) in the treatment of variety of cancer including colon cancer (see para. 71) . Bermudes et al teach delivering attenuated tumor-targeted strain of Salmonella VNP20009 carrying an asd plasmid which expresses a hexahistidine-endostatin fusion protein demonstrating the inhibitory effect of the hexahistidine-endostatin expressing attenuated tumor targeted Salmonella on the growth of DLD1 human colon carcinoma (see example 13, para. 380-388). Furthermore, Bermudes et al embraced the potential of delivering transgene under the control of CEA promoter (para. 271) and exemplified genetically modified attenuated Salmonella VNP20009 that is specifically retained in the tumor and not in liver suggesting specific binding and infection of microorganism to cancer cells after delivery to the microorganism (see example 16) meeting the limitation of claims 33 and 65). Furthermore, Bermudes et al disclosed a number of therapeutic agent could be delivered to the tumor cells including a pro-drug converting enzyme; an antisense molecule (see para. 58, 189-193) meeting the limitation of claims 29 and 60. The genetically modified Salmonella typhimurium disclosed by Bermudes et al and those embraced by the instant claims appear to be structurally same. Similarly, Szalay et al also disclose availability of another attenuated strain of *Salmonella typhimurium* (SL7207 see para. 96) that may be genetically modified to target variety of cancer including bladder, breast, prostate tumors, brain and colon (see para. 68 and figure 9-12). Although, Bermudes et al embraced the expressing in attenuated Salmonella VNP20009 to target variety of tumor including colon cancer but differed from claimed invention by not disclosing expressing an antibody or an neaoplasm specific antigen on the surface of the microorganism.

However, prior to instant invention, displaying a functional scFv antibody fragment to the outer surface of bacterium was known in prior art. For instance, Francisco et al cure the deficiency by teaching a method for displaying a functional

scFv antibody fragment to the outer surface of E. coli microorganism that is capable of binding to an antigen with high affinity that also transformed with a construct comprising chloramphenicol-resistance gene (see material and methods page 10444, col. 2, para 1 and 10445, col. 2, para. 2 and 3). Although, Francisco et al taught a method to display scFv antibody fragment specific for digoxin on the surface of E. coli that is also transformed with a nucleic acid but differed from claimed invention by not disclosing displaying neoplasm specific antigen.

Wu provided guidance with respect to the sequences of anti-CEA diabody T84.66VL-GS8 linker-VH (T84.66-GS8) or scFv T-84.66VL-GS18 linker-VH (T84.66-GS18) (see page 23, col. 1, last para. bridging to col. 2). Wu et al reported producing stable dimers of anti-CEA scFv that have excellent tumor targeting properties: substantial and persistent tumor uptake coupled with rapid clearance from blood and normal tissues (see Figure 7, table 3 and page 35, col. 1, para. 2).

Accordingly, in view of the teachings of Bermudes et al/ Szalay, Francisco and Wu, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention to modify the genetically modified attenuated strain of *Salmonella typhimurium* (VNP 200009 or SL7207) to expresses a functional scFv antibody fragment on the outer surface such as CEA antibody that has excellent tumor homing properties. One of ordinary skill in the art would be motivated to express functional scFv antibody fragment of CEA with reasonable expectation of success in achieving the predictable results as the Artisan was well aware of the required method for displaying a functional scFv antibody fragment to the outer surface of another microorganism as evident from the teaching of Francisco. It would have been obvious to one of ordinary skill in the art to substitute *E.Coli* with another microorganism such as attenuated strain of *Salmonella typhimurium* (VNP 200009 or SL7207) for displaying CEA scFv antibody on the surface of the microorganism as Wu taught required sequences of anti-CEA diabody that would have resulted in stable dimers of anti-CEA scFv. It is noted that there is nothing in

the art to demonstrate that the artisan would not expect them to work, as the method to display scFv antibody and the required sequences fall into the general requirements for displaying an antibody on the surface of the microorganism, as in Francisco. Hence, it would appear that Applicant's contribution to the art is simply to claim scFv antibody sequences that are expressed on the surface of a known attenuated microorganism for specifically targeting tumor. Furthermore, KSR has already stated that motivation need not be specific, and only in the case of an infinite number of variants is a specific variant non-obvious. Given that one of ordinary skill in the art was well aware of the results of displaying scFv antibody, the requirements for expressing antibody on the surface of the microorganism, and was already able to express CEA antibody that specifically localized in tumor. Hence, it is prima facie obvious to one the artisan to express CEA scFv antibody on the surface of genetically modified attenuated strain of microorganism disclosed by Bermudes et al/ Szalay to obtain microorganism that displays CEA scFv antibody as disclosed in the instant application. One who would practiced the invention would have had reasonable expectation of success because that method of displaying scFv antibody and sequences for anti-CEA diabody and linker requirements were already known in the art in an obvious manner to display antibody on the surface of an microorganism, as the Artisan already recognized such method to display antibody on the surface of attenuated strain of *Salmonella typhimurium*. Thus, it would have only required routine experimentation to modify the microorganism disclosed by Bermudes et al/ Szalay to display CEA scFv antibody as required by instant invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Withdrawn-Double Patenting

Claims 1-29, 33-61 and 65 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-29, 33-61 and 65 of copending Application No. 11/213499 (US patent publication no. 20060083716) is withdrawn in view of abandonment of application no 11/213499 (US patent publication no. 20060083716).

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Dillon et al (US Patent no 5, 395,750, dated 3/7/1995) teaches method of producing protein and expressing on the surface of microorganism that binds to predetermined antigen.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh
AU 1632

/Thaian N. Ton/
Primary Examiner, Art Unit 1632